Computational Modeling of Complex Physiological Flows : Malaria and Gastric Emptying

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論 文 内 容 の 要 旨

Chapter 1　Introduction

Computational fluid dynamics has been contributed to our understandings of physiological flows, especially blood flows in large arteries. Although blood consists of plasma and cells, including red blood cells, white blood cells, and platelets, in large arteries, rheological effects of these cells can be ignored, and blood is simply modeled as a continuous fluid. Conventional numerical methods for incompressible Newtonian fluids have been successfully adapted to this problem. CFD analysis of arterial blood flows is now common, and medical doctors also use CFD analysis for clinical diagnosis of aneurysms. In contrast to such a progress in CFD studies of arterial blood flows, CFD of other complex physiological flows has not been well developed. Physiological flows are in general, complex fluid mechanics problems, involving moving boundaries. However, numerical methods for simulating moving boundary problems remain to be established, and new numerical methods are still being developed. As a consequence, many physiological flow problems have not been well studied using CFD. The primary objective of this study is to advance computational modeling and simulation of complex physiological flows with moving boundaries. For this objective, we focused on two challenging problems in physiological flows: microcirculatory blood flow in malaria infection, and gastric emptying in the digestive system.

Chapter 2　Computational modeling of *Pf*-IRBC adhesion on a wall

In chapter 2, we presented computational model of a red blood cell infected by *Plasmodium falciparum* (*Pf* -IRBC) adhesion in microcirculatory blood flow. We developed a coupling method of the biochemical interactions of ligand-receptor bindings with the solid and fluid mechanics of

the *Pf* -IRBC. The finite element method (FEM) and the boundary element method (BEM) are used for solving the solid and fluid mechanics. The biochemical interactions are modeled by Bell model with a Monte Calro method, and coupled with the FEM and BEM. We investigated the effects of bond type, i.e., slip, ideal, and catch bonds, on the rolling motion of *Pf* -IRBCs. The *Pf* -IRBC model exhibited firm adhesion, flipping motion, and tank-treading motion, depending on the applied shear rate for slip bonds. The behavior for catch bonds resembled that for slip bonds, except for an additional "catch" state at high shear stress. We compared the numerical results with previous experiments for ItG- and A4- infected cells. We found that the interaction between PfEMP1 and ICAM-1 could be a nearly ideal bond, with a dissociation rate ranging from 30 s^{-1} to 100 s^{-1}.

Chapter 3 Computational modeling of *Pf*-IRBC adhesion in microvessels

In chapter 3, we investigated the behavior of *Pf* -IRBC in microvessels using a numerical model. BEM is only applied to simple domains, such as infinite domains and semi-infinite domains. To simulate RBCs in microvessels, the lattice Boltzmann method (LBM) is employed for fluid mechanics. Cytoadhesion of Pf -IRBCs is predominantly found in postcapillary venules, rather than in arterioles. However, factors influencing this phenomenon remain unclear. We showed that, once a Pf -IRBC adheres to the vascular wall, the Pf -IRBC can withstand even arteriole shear stresses, and exhibits either rolling or firm adhesion. We also performed a simulation of the multistep process of cytoadhesion, consisting of flow, margination, capture, and rolling or firm adhesion. This multistep simulation suggested that a lower probability of contact with the vascular wall at high shear rates may diminish adherent Pf -IRBCs in the arterioles.

Chapter 4 Computational modeling of gastric emptying

In chapter 4, we presented a 3D numerical modeling of gastric emptying and simulated fluid dynamics using an anatomically-realistic geometry of the stomach and duodenum. For stable simulation, we used the multiple-relaxation-time lattice Boltzmann method (MRT-LBM) to solve gastric flow. We investigated how the coordination between the terminal antral contraction and the pyloric opening/closure affects the mixing and emptying of liquid contents. We showed that peristaltic contractions at the proximal stomach promote gastric emptying with an emptying rate of 3-7 ml/min under hydrostatic equilibrium. The duration of the pyloric closure and its coordination with the terminal antral contraction had a minor effect on gastric mixing. When the pylorus is not able to close, emptying rate increased to 10-30 ml/min, but instantaneous retrograde flow from the duodenum to the antrum occurred at an antral relaxation phase. Our results also suggested that impaired coordination is able to cause even a negative emptying rate, particularly when the pylorus is only opened at the antral relaxation phase.

Chapter 5 Conclusion

In this study, we developed computational models of Pf -IRBC adhesion in microcirculatory blood flow and gastric emptying. These two problems are most challenging problems for numerical modeling and simulation. Hence, the methods developed in this study may be applicable to other physiological flow problems. We also provided new insights into these complex physiological flows: why Pf -IRBCs predominantly adhere to the vascular wall in post-capillary venules, and how the coordination between TAC and the pyloric closure affects the mixing and emptying of liquid contents. The computational models and findings presented in this thesis may be helpful for understanding these physiological flows. These flows in real conditions, i.e. in our body, are of course more complex. Vessel geometries, irregular wall surface, and receptor and ligand distributions should be considered in real microcirculation. In the case of real gastric flow, a decrease of gastric volume and intestinal wall motion may affect gastric emptying. The gastric juice and solid components of food may also be important factors. We hope that this study stimulates future computational and experimental studies of physiological flows